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Obesity and Lifestyle Changes: A Global Risk Factor for Cancer

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Abstract

Obesity is a well-established risk for numerous cancers. It is found to significantly increase the risk of developing post-menopausal breast, colorectal, endometrial, kidney, esophageal, pancreatic, liver, and gallbladder cancer. In fact, studies have shown that excess body fat can lead to an approximate 17% higher risk of cancer-specific mortality. Moreover, research has also linked obesity to other common cancers such as breast cancer, colorectal cancer, esophageal cancer, gallbladder cancer, uterine cancer, pancreatic cancer, and liver cancer. Not only does obesity increase the risk of developing these cancers, but it can also impact the outcome and treatment choices for individuals diagnosed with cancer. In fact, Obesity is estimated to be responsible for about four to eight percent of all cancers. Understanding mechanisms at work by which obesity contributes to the development of cancer is complex and still not fully understood. However, changing lifestyles such as adopting a healthy diet, engaging in regular exercise, and behavior therapy have been shown to be effective interventions. In some cases, weight loss surgery and drug therapy may be considered for a specific group of cancer survivors who are also dealing with obesity. In conclusion, this review emphasizes the importance of recognizing the epidemiology and risks associated with cancer in obese individuals. It also underscores the significance of managing obesity through various interventions to reduce the incidence and recurrence of cancer.

Keywords: Cancer, Boby mass index, Obesity, Overweight

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Introduction

Among many chronic diseases associated with obesity are coronary artery disease, diabetes, high blood pressure, disease of the joints, sleep problems, and mental health disorders. Obesity, being a prevalent condition, is also closely linked to some of the major chronic diseases. Furthermore, there is increasing evidence to suggest that obesity would increase the risk of various types of cancer affecting organs and blood cells [1-3]. Cancers such as breast cancer, colon cancer, rectal cancer, esophageal cancer, stomach cancer, gallbladder cancer, uterine cancer, pancreatic cancer, ovarian cancer, and esophageal cancer are also associated with obesity. As far as obesity and cancer are concerned, the relationship is rather complicated [4, 5]. Furthermore, obesity is not only associated with an increased risk of cancer, but it may also be associated with greater chances of recurrence and mortality among cancer survivors. To enhance cancer outcomes, it is crucial to manage obesity as early as possible in patients with early-stage cancer as a way to enhance quality of life [6-8].

In the last ten years, there has been emerging evidence linking obesity to a higher risk of cancer and poorer outcomes. Additionally, recent studies have shed light on the importance of addressing obesity in cancer patients, leading to the approval of new drugs that are not only more effective but also safer compared to older agents for managing weight in adults with obesity. It is important to note that there is a growing number of ongoing prospective studies that focus on different aspects of obesity in cancer patients [9, 10]. The objective of these studies is to provide a more profound understanding of the intricate connection between cancer and obesity [11].

This comprehensive review aims to offer readers up-to-date and comprehensive information about the complex relationship between obesity and cancer. To achieve this goal, the paper initially explores the definition of obesity and its implications, examines the epidemiology of obesity and cancer in the general population, and discusses the utilization of innovative technology in measuring obesity and body fat distribution [12]. Furthermore, it investigates potential biological mechanisms that contribute to the development of cancer in individuals with obesity, revealing the underlying factors that drive this association.

Moving forward, the review highlights recent data that underscore the strong inverse correlation between obesity and cancer outcomes. This includes an elevated risk of recurrent disease and complications

related to treatment, which can negatively impact patient prognosis. The paper then proceeds to assess the management of obesity through various strategies in cancer survivors, emphasizing the significance of weight reduction as an essential complement to cancer treatment. Weight reduction not only reduces the risk of disease recurrence but also lowers the likelihood of developing a new primary cancer related to obesity, underscoring its potential as a preventive measure [13, 14].

Finally, the review summarizes ongoing and promising clinical trials addressing obesity in cancer survivors [15]. As a result of these trials, we will be able to develop more effective management strategies for cancer in the future by better understanding how obesity affects cancer outcomes. Optimizing patient care and improving outcomes for cancer and obesity patients can be achieved by expanding our knowledge in this field.

Method

In order to carry out an analysis of the literature, PubMed and Google Scholar were used with the intention of conducting a literature review. The reference lists of relevant articles were also consulted to find relevant materials, as well as guidelines and position papers from professional societies and organizations. Due to the extensive nature of this paper, it was considered impractical to conduct a formal literature search [1]. The search primarily focused on English papers published in the last ten years up until April 2023, specifically investigating the epidemiology, pathogenesis of cancer in relation to obesity, cancer incidence, the risk of recurrence in obesity, and the management of obesity. This review identifies key papers using multiple independent searches using different keyword combinations alongside "obesity" and "cancer" to encompass the various aspects of cancer and obesity.

Obesity Measurement

Obesity is defined by excess body fat. Several clinical terms are used to describe people with excessive body fat that put them at a high risk of poor health. "Obese" and "obesity" are typically used to describe these individuals. As a matter of fact, WHO (World health Organization) recognized obesity as a disease during late1940s, but it gained a greater significance in the late 20th century when its relationship with serious illnesses was established [16]. WHO definition of obesity is "excessive accumulation of fat to the point where it adversely impacts health" (Table 1). There are a number of factors that contribute to obesity, including genetic, environmental, socioeconomic, and behavioral factors [17]. An indicator of excess body fat is the body mass index (BMI). Hence, it is generally agreed that obesity is typically defined as a BMI or weight to height ratio equal to or greater than 30 kg/m^2. The BMI range of 25 to 29 kg/m^2 is considered overweight for people with this BMI. The BMI ranges from 30.0 to 34.9 kg/m^2 in class I; 35.0 to 39.9 kg/m^2 in class II; and 40 kg/m^2 or higher in class III, or extreme obesity. As well as having a high waist-to-hip ratio, obesity is commonly referred to as being overweight or obese. Compared with BMI or waist circumference, abdominal obesity, which is defined as a waist-to-hip ratio exceeding 0.90 for men and 0.85 for women, is a better indicator of cardiometabolic risk [18, 19]. It has also been found that waist circumference and waist-to-hip ratio are as effective as BMI in predicting cancer risk, if not better [20].

Table 1: Measurement of obesity in adults (Adapted from WHO).

Classification	BMI (kg/m^2)	
	Principal cut-off points	Additional cut-off points
Underweight	<18.50	<18.50
Severe thinness	<16.00	<16.00
Moderate thinness	16.00 - 16.99	16.00 - 16.99
Mild thinness	17.00 - 18.49	17.00 - 18.49
Normal range	18.50 - 24.99	18.50 - 22.99
		23.00 - 24.99
Overweight	≥ 25.00	≥ 25.00
Pre-obese	25.00 - 29.99	25.00 - 27.49
		27.50 - 29.99
Obese	≥ 30.00	≥ 30.00
Obese class I	30.00 - 34.99	30.00 - 32.49
		32.50 - 34.99
Obese class II	35.00 - 39.99	35.00 - 37.49
		37.50 - 39.99
Obese class III	≥ 40.00	≥ 40.00

Epidemiological studies commonly employ anthropometric measures to evaluate body fat when researching obesity. Nonetheless, it is crucial to acknowledge the limitations of these measures. Consequently, scientists and researchers have explored various alternative methods to assess body fat composition and distribution [21]. For example, dual energy X-ray absorptiometry is a widely used test to directly measure overall body fat and its regional distribution. According to, an abnormal indication of body fat is more than 25% in men and more than 30% in women [21-23]. In addition, bioelectrical impedance, ultrasound, computed tomography scans, and magnetic resonance imaging scans have also been used.

Obesity and Cancer-biological Relationship

Obesity is a widely recognized predisposing factor for numerous malignancies, particularly breast and colorectal cancer. Adipose tissue and its surrounding environment may have a role to play in the formation of cancer, the spread of metastases, and the advancement of the disease. Nevertheless, the exact mechanism responsible for the development of cancer is intricate and still not completely comprehended [24]. Disturbed secretion and metabolism of fatty acids, modifications in the extracellular matrix, the release of anabolic and sex hormones, immune system imbalance, persistent inflammation, and alterations in the gut microbiome have all been connected with the formation of cancer, the spread of metastases, and the progression of cancer in individuals with obesity [25]. It is probable that different mechanisms contribute to the occurrence of various types of cancer.

Dysfunction in adipose tissue caused by obesity can have negative effects on the development, advancement, and recurrence of tumors. Excessive accumulation of fat results in the production of proinflammatory cytokines, sex hormones, and lipid metabolites by adipocytes. This also leads to impaired profiles of cytokines or adipokines derived from adipocytes, causing insulin resistance. Moreover, this dysfunction affects the extracellular matrix by causing remodeling and fibrosis. Additionally, it leads to the formation of cancer-associated adipocytes and influences microbial metabolism. Furthermore, these changes in adipose tissue impact the progenitors of adipocytes, triggering inflammation and altering the micro-environment [26]. It is through these various mechanisms that obesity-induced dysfunction in adipose tissue contributes to the initiation, growth, and reappearance of tumors (Figure 1).

Obese individuals face a potential risk of developing cancer due to three main biological processes. One of these processes involves the concept of adipose tissue functioning as an "organ", capable of releasing chemical substances and enzymes [27, 28]. More specifically, this process refers to the higher production of estradiol from androgens

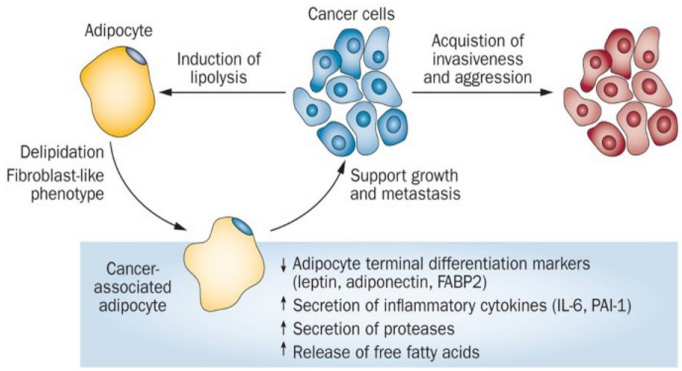

Figure 1: Obesity and cancer mechanism.

in peripheral adipose tissue, which is facilitated by the presence of aromatase. Excessive estrogen production by adipose tissue has been associated with an elevated likelihood of developing various types of cancer, including breast, endometrial, ovarian, and others [29].

An elevated BMI leads to hyperinsulinemia, which not only enhances the normal growth function of insulin but also prolongs the activity of insulin-like growth factor-1 (IGF-1). Obese individuals often have elevated levels of insulin and IGF-1 in their blood. Insulin resistance, a well-known risk factor for cancer, results in excessive insulin production or hyperinsulinemia, which occurs prior to the onset of type 2 diabetes. Elevated insulin and IGF-1 levels may contribute to the development of colon, renal, prostate, and endometrial cancer [30].

The final component of the system is associated with the inflammatory ambiance developed due to the modified release of various adipokines (peptide hormones) by fatty tissue, particularly heightened amounts of leptin, a powerful inflammatory, proliferative, and anti-cell death substance [31, 32]. Adiponectin, an additional adipokine with anti-proliferation characteristics, is deficient in overweight individuals who maintain a favorable body mass. Surplus fat tissue causes adipocyte enlargement and cellular demise, leading to the persistent, asymptomatic inflammation of fatty tissue. Numerous preclinical investigations provide evidence that chronic inflammation in adipose tissue initiates carcinogenesis and the advancement of malignancy. Individuals who are overweight exhibit modified levels of inflammatory cytokines, including IL-6, TNFα, and C-reactive protein [33-37]. Obese adults are more likely to suffer from chronic inflammation-induced ailments, including gallstones and non-alcoholic fatty liver disease, caused by the accumulation of fat in the liver. These factors induce oxidative stress, resulting in DNA damage and an increased susceptibility to the development of biliary tract, liver, and other tumors [38]. The presence of obesity may also increase the risk of cancer in a number of ways, including lowering the immune system of the tumor and altering the biomechanical properties of the tissue where the tumor grows [39-41]. Adipokines, modulation of immune cells and systemic inflammation, angiogenesis, metabolic alterations, modulation of the extracellular matrix, and extracellular vesicles like exosomes have been associated with metastasis.

Fat Distribution, Metabolic Syndrome, and Cancer

Metabolic syndrome is strongly linked to a higher BMI, which is characterized by elevated levels of insulin, glucose, triglycerides, and residual cholesterol, as well as decreased levels of high-density lipoprotein cholesterol. Insulin resistance and dyslipidemia are influenced by the amount and location of adipose tissue [42]. The negative metabolic consequences of being overweight are evident during childhood and may worsen over time. Furthermore, excessive body fatness is associated with elevated systolic and diastolic blood pressure and weakened immune function due to increased levels of pro-inflammatory substances like interleukin-6 [43-44].

The body fat distribution in adults is diverse, and BMI alone fails to fully capture the intricate relationship between surplus fat and the likelihood of cancer and its progression. The distribution of body fat is now recognized as a crucial factor in predicting the adverse health consequences of obesity, with visceral fat posing a greater risk compared to subcutaneous fat. Gluteofemoral obesity (fat accumulation in the lower body), abdominal obesity (fat accumulation in the upper body), and visceral fat depots exhibit distinct metabolic characteristics related to fatty acids [45]. The metabolic consequences of being overweight are affected by the selective disturbance of these fat deposits [46]. For instance, the negative impacts of fat distribution on well-being are significantly influenced by the disturbance of fat breakdown in the upper body, specifically in adipose tissue that is not part of the digestive system. Conditions such as type II diabetes, high blood pressure, insulin resistance, abnormal lipid levels, and early death due to cardiovascular diseases have all been clearly associated with upper body obesity, especially when there are high levels of visceral fat [47]. Moreover, there is evidence suggesting that having excess fat in the central area of the body may be a more accurate indicator of the risk of developing any type of cancer than overall body size [48-50]. According to research on Mendelian randomization, the metabolic risk factors with the highest association to cancer linked to fat are those individuals with higher levels of insulin when fasting (Figure 2).

Epidemiological Perspective

The global prevalence of obesity has almost tripled since 1975, with an alarming increase in the number of overweight and obese children under the age of five in 2020. If current patterns persist, it is projected that by 2025, there will be a staggering 2.7 billion overweight adults, over 1 billion individuals classified as obese, and 177 million people categorized as extremely obese. Additionally, it is

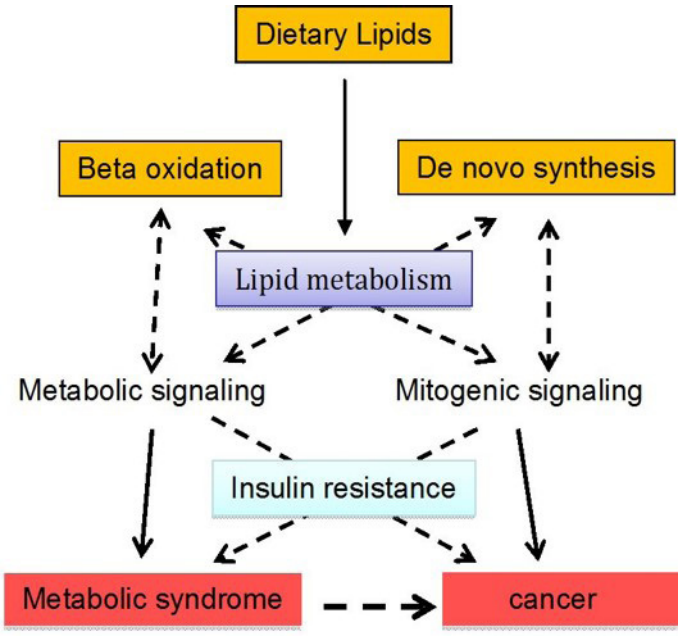

Figure 2: Inter-relationship between lipid metabolism, metabolic syndrome, and cancer.

expected that approximately 38% of the adult population worldwide will be overweight by 2030, while an additional 20% will be obese. A comprehensive meta-analysis comprising of 230 studies and over 30 million participants has demonstrated a direct correlation between excess body weight and higher all-cause mortality rates. Moreover, obesity is estimated to contribute to approximately 4-8% of all cancer cases globally, with a higher incidence in high-income countries compared to low-income nations. In the United States, obesity is believed to account for approximately 4.7% of new cancer cases in men and 9.6% of new cases in women. However, the association between cancer and excess body weight varies depending on the specific type of cancer. For instance, over half of all liver or gallbladder cancers in women and almost half of all endometrial cancers in women are attributable to obesity. Similarly, nearly half of all liver or gallbladder cancers and over 30% of all adenocarcinomas are linked to obesity [1]. It is estimated that approximately 21% of obesity-related cancers in the American population could be prevented if individuals maintained a healthy body weight or a BMI below 25. Furthermore, among cancer survivors aged 20 years or older, over one-third are classified as obese, and another one-third are reported to be overweight [51].

Risk of Cancer in Overweight Patients

Those who gain weight are more likely to develop post-menopausal breast, colorectal, endometrial, renal, and high-risk prostate cancers. Several studies have linked BMI to the most common site-specific cancers, including 166,955 new cancer cases among 5.24 million individuals. Mendelian randomization studies have shown that an increase in body fat would increase the chances of developing cancers of the ovary, the esophagus, the stomach, the pancreas, the kidneys, the colorectal, the endometrium, and other organs [52]. Observational epidemiology employs Mendelian randomization to assess causation by using genetic variations relevant to potentially modifiable exposures as proxies.

There are several reports that revealed compelling findings regarding the correlation between obesity and 12 distinct types of cancer [53]. The cancers that the obese population is more susceptible to include post-menopausal breast, colorectal, endometrial, esophageal, pancreatic, renal, liver, stomach, gallbladder, ovarian, thyroid, multiple myeloma, and meningioma. It is moderately likely that obesity causes cancers of the oral cavity, pharynx, larynx, prostate, male breast, as well as diffuse large B-cell lymphoma. In addition to the two most common cancers, breast and colorectal cancer, there is a high risk of pancreatic, esophageal, and gallbladder cancers [54, 55]. The extensive analysis of systematic evaluations and meta-analyses thoroughly investigated the link between excess body fat and the probability of developing cancer. The results varied, ranging from a 9% surge (RR 1.09, 95% CI 1.06 to 1.13) in the risk of rectal cancer among males to a 56% surge (1.56, 1.34 to 1.81) in the risk of cancer in the biliary tract system for every 5 kg/m^2 increase in BMI. Furthermore, women who never underwent hormone replacement therapy encountered an 11% increase in the risk (1.11, 1.09 to 1.13) of post-menopausal breast cancer for every 5 kg of weight gained in adulthood, while the risk of endometrial cancer escalated by 21% for every 0.1 rise in the waist-hip ratio (1.21, 1.13 to 1.29) [1].

The relationship between obesity and breast cancer is complex, with differing associations observed in pre- and post-menopausal women. In pre-menopausal women, the connection between obesity and breast cancer is either contrary or neutral. There is, however, a positive correlation in post-menopausal women, particularly those with hormone-positive breast cancers. Dual-energy X-ray absorptiometry has demonstrated that women with normal BMIs, but high levels of total body fat are at a higher breast cancer risk. The hazard ratio for all invasive breast cancer is 1.89 (95% CI, 1.21 - 2.95), and for hormone-receptor positive breast cancer, it is 2.21 (95% CI, 1.23 - 3.67). As trunk fat increases by 5 kg, the risk of hormone receptor-positive breast cancer rises by 56%. All these factors have been associated with obesity-related postmenopausal breast cancer, including insulin resistance, inflammation of breast adipose tissue, inflammation of breast adipose tissue, elevated expression of aromatase enzyme, and higher levels of leptin. People with Lynch syndrome have been found to be more likely to have colorectal cancer if they are obese [56]. An analysis of four studies found a twofold increase in colon and rectal cancer risk among obese men with Lynch syndrome. No significant risk of colorectal cancer was observed in women. MLH1 germline mutations increased the risk of colorectal cancer by 49% compared to healthy weight subjects (Figure 3).

Outcomes of Obesity and Cancer

There is evidence to suggest that not only does obesity raise the chances of developing cancer, but it may also heighten the likelihood of cancer returning in the early stages and be connected to poorer outcomes. Communication between cancer cells and adipose tissue through high levels of insulin, inflammatory cytokines, adipokines, and proteins in the extracellular matrix encourages the spread of cancer [50]. Specifically, the accumulation of visceral adipose tissue in the abdominal area, known as central obesity, has been associated with cancer progression [57].

An examination of different cohort studies we conducted a systematic review and meta-analysis, which indicated that being overweight and obese is linked to a higher chance of death from any cause [58]. Furthermore, obesity has been connected to negative results in certain types of cancer. However, the connection or outcomes of obesity with cancer is not fully comprehended. The variation among different types of cancer, and even within subcategories, introduces differences when studying a cause-and-effect relationship [59, 60]. In a systematic review and meta-analysis of 203 cancer research studies, obesity was found to be associated with a greater risk of mortality in general and mortality in cancer-related conditions. The risk of death from excess weight is 14% greater. The risk of cancer is 17% higher. Furthermore, overweight people are 13% more likely to experience

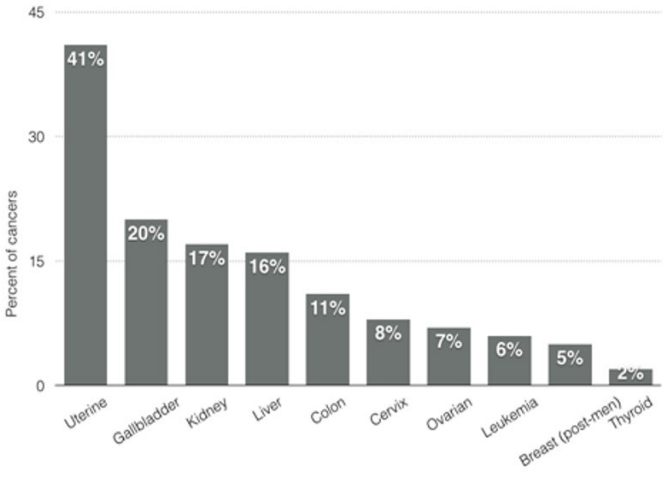

Figure 3: Percentage of cancers linked to overweight and obesity.

cancer recurrence. Obese individuals diagnosed with breast, colorectal, and uterine cancer typically show unfavorable survival rates. Obesity is associated with increased cancer-specific mortality in patients with breast, colorectal, prostate, and pancreatic cancers, as well as higher recurrence rates in patients with breast, colorectal, prostate, and gastroesophageal cancers [61]. Conversely, overweight patients diagnosed with melanoma, lung, and kidney cancer generally exhibit better survival rates compared to non-obese patients.

Obese individuals suffering from various cancers may experience unsatisfactory outcomes due to multiple factors, such as an underlying metabolic syndrome, hormonal influences linked to certain endocrine-dependent cancers, inadequate physical activity, and suboptimal treatment [17]. It is noteworthy that the concept of dose-capping in obese patients, discussed further below, is applicable to all types of cancer [62]. Furthermore, other conventional treatments have been associated with unfavorable results in obese cancer patients. For instance, surgical resections in obese individuals have been found to be associated with a higher occurrence of post-operative complications, including wound infection, prolonged operative duration, and an increased risk of blood loss. Patients with gastrointestinal cancer who experience operative complications following radical surgery have a lower long-term survival rate [63, 64]. As a result, radiation therapy has been shown to produce poorer outcomes for obese patients owing to the difficulties associated with daily setup and the limited movement of the tumor within their adipose tissues.

Pancreatic cancer

It has been shown that both muscle loss and dysfunction, or increased fat mass or obesity, are associated with poor outcomes in pancreatic cancer. Several studies have demonstrated that obesity is associated with a 28% increase in pancreatic cancer-related mortality [1]. There was a 10% increase in mortality with every kg/m^2 increase in BMI, according to a systematic review and meta-analysis of 13 studies.

Colorectal cancer

The patient's BMI has been found to impact the prognosis of colorectal cancer as well. Research indicates that individuals who are obese are more likely to present with advanced-stage cancer (II or III) and have a higher number of lymph nodal metastases (N > 3) [21]. There is evidence to suggest that obesity before diagnosis is linked to an elevated risk of disease-related death and reduced overall survival. Furthermore, obesity has been associated with a 14% increase in both colorectal cancer-specific and overall mortality rates. An analysis of 58,917 patients in 16 prospective cohort studies showed an increased risk of mortality overall and 22% for colorectal cancer-specific death in obesity before cancer diagnosis [65]. According to a recent research study, having a BMI of 35 after a colorectal cancer diagnosis increased all-cause mortality by 13% [66].

Prostate cancer

A correlation has been found between a rise of 5 kg/m^2 in BMI and a 21% rise in the likelihood of the biochemical recurrence of prostate cancer. It was concluded from an analysis of 59 studies involving 280,199 patients that obesity increases the risk of death from prostate cancer by 19% and the overall mortality rate by 9% [67, 68]. When BMI increases by 5 kg/m^2, prostate cancer-specific mortality increases by 9% and overall mortality increases by 3%. Compared with obese men without prostate cancer, men with late detection, aggressive cancer, and poorer treatment outcomes are more likely to undergo radical prostatectomy and have positive resection margins.

Breast cancer

Not only does obesity raise the likelihood of recurrent breast cancer, but it also heightens the chances of significant coexisting illnesses and negatively impacts the quality of life for survivors of breast cancer [69, 70]. A review of 82 research papers on breast cancer survivors showed that obesity increased the risk of death from breast cancer and respiratory disease by 35% and 41%, respectively. The results of 13 studies that included 8,944 women with triple negative breast cancer showed that overweight women had a shorter period of disease-free survival (HR = 1.26; 95% CI: 1.09 - 1.46) and overall survival (HR = 1.29; 95% CI: 1.11 - 1.51) than women with normal weights [71].

Studies indicate that approximately 30 - 50% of women experience a weight gain exceeding 5% of their body weight during and following chemotherapy, which can persist for up to 5 years after diagnosis. The timing of obesity onset in relation to diagnosis, as well as menopausal status, demonstrate varying patterns [72, 73]. Patients classified as obese (BMI > 30) one year prior to diagnosis have a higher risk of breast cancer-specific mortality, regardless of menopausal status. Similarly, patients who are obese at the time of diagnosis also face an increased risk of mortality, although to a lesser extent compared to pre-diagnosis studies. Post-diagnostic obesity has been found to be an unreliable indicator of recurrence. For instance, an analysis of seven studies revealed that a weight gain of 5 kg within 6 months of diagnosis was associated with a 31% worse prognosis; conversely, no significant trend was observed with weight loss. Weight gain after breast cancer diagnosis was associated with a 12% higher risk of all-cause mortality, according to a systematic review and meta-analysis of 12 studies involving 23,932 survivors [1]. This increased mortality risk (HR of 1.23) was evident for a weight gain of 10.0% [74-76]. As a result of increased peripheral aromatase activity, obesity may adversely affect adjuvant aromatase inhibitor effectiveness for women with hormone receptor-positive breast cancer.

Endometrial cancer

Endometrial cancer is significantly linked to obesity and is also associated with poorer outcomes in women diagnosed with the disease. Women who have a high BMI and waist circumference both before and after being diagnosed with endometrial cancer have lower rates of disease-free survival and overall survival [77]. A comprehensive analysis of 46 studies revealed that obesity increases the risk of all-cause mortality by 34% and the risk of cancer recurrence by 28% in women with endometrial cancer.

Adverse Effects due to the Treatment:

There is a rise in the number of negative effects caused by cancer treatment due to obesity [78]. Lymphedema is a complication that arises from surgery and radiation on the axillary lymph nodes for women who have breast cancer. The likelihood of developing lymphedema is significantly higher for women with breast cancer who have higher body weights compared to women with normal body weights. Similarly, peripheral neuropathy caused by chemotherapy is a common side effect of various anti-cancer drugs and has been linked to a reduction in the quality of life [1]. There is evidence that obese patients are more likely to develop taxane and platinum-related neuropathy. The risk of cardiotoxicity associated with excess body fat has also been shown to be high in recent studies [79, 80]. The results of a meta-analysis of 15 studies identified an association between obesity and a 47% higher risk of cardiac toxicities for women treated with anthracyclines and trastuzumab for early-stage breast cancer [81].

Obesity also increases radiation therapy-related toxicities. There is 11% risk of radiation-related acute dermatitis in breast cancer survivors with a BMI of >25 in a systematic review and meta-analysis of 38 studies (Table 2). According to available studies, cancer patients with high BMIs are more likely to suffer surgical complications [82].

Selecting a Proper Treatment

Specific types of cancer therapy may be affected by obesity. High BMIs do not negatively influence treatment decisions regarding adjuvant chemotherapy in women with breast cancer but may influence immediate reconstruction of the breast following mastectomy. Obese individuals might be given a dose that is lower than the weight-based dose due to concerns about toxicity [83-87]. This dose restriction, known as dose capping, may have negative effects on the prognosis and outcomes of obese cancer patients, particularly those receiving adjuvant chemotherapy for early-stage cancer or definitive treatment for highly chemosensitive cancers like aggressive lymphoma [88, 89]. The clinical guidelines discourage dose capping in obese patients and advocate for administering the full weight-based chemotherapy dose.

Management of Obesity in Cancer Survivors

As a result of cancer diagnosis and treatment, many cancer survivors gain weight. Besides increasing recurrence risks in some cancers, obesity also increases the risk of diabetes, cardiovascular disease, and poor quality of life. Cancer survivorship care should include interventions aimed at weight reduction. Several cancers, including some of the most prevalent types (breast, lung, bowel, and kidney), have been associated with physical activity negatively [90, 91]. In order to prevent cancer, an active lifestyle can either enhance metabolic control, or prevent adult weight gain, either directly or indirectly.

A significant reduction in weight is achieved when structured exercise is combined with dietary support to lose weight. It is especially effective in reducing insulin resistance, circulating levels of sex hormones, leptin, and inflammation markers linked to common cancers [92]. A number of cancer guidelines advise survivors to maintain a healthy weight, yet there is limited evidence on which weight loss method to suggest. Lifestyle interventions encompassing diet, physical activity, and behavioral therapy are the cornerstone of approaches related to modifying one's lifestyle. Pharmaceutical and surgical interventions have not been extensively researched in cancer survivors [93]. A Cochrane meta-analysis involving 20 studies with 2,028 breast cancer survivors assessed the impact of various approaches to losing body weight among overweight or obese breast cancer survivors, and discovered that weight loss interventions, particularly those that incorporate diet, exercise, and psychosocial interventions, led to reductions in body weight, body mass index, waist circumference, and improved overall quality of life [94] (Figure 4).

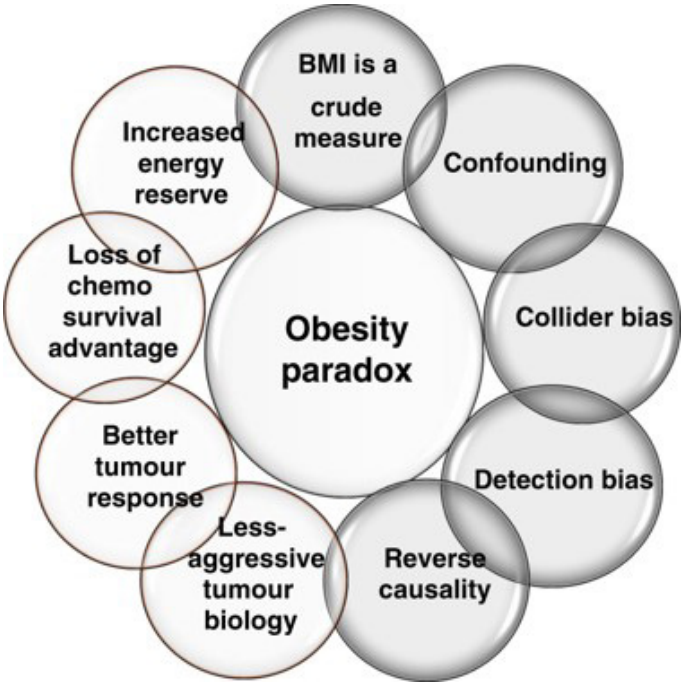

Figure 4: Possible explanations for obesity paradox.

Behavior therapy

An active lifestyle and healthy eating habits are promoted through the use of various techniques and strategies in behavior therapy. As part of this process, the participant logs their eating, calorie intake, and physical activity, modifies the environment in order to avoid overeating, creates a realistic exercise plan, and sets realistic goals, among other things [95, 96].

Diet

There is evidence that weight loss occurs when the caloric deficit is consistent no matter which type of diet is followed. The POUNDS LOST trial assessed short-term and long-term weight loss among four dietary groups with a deficit of 750 calories per day over a two-year period

Table 2: Methods for the estimation of body fat composition and its distribution.

Methods	Technical principles	Potential benefit and drawbacks
Anthropometric measurement	Manual measurement of weight to height ratio (BMI), waist-hip ratio, waist circumference, arm circumference, skinfold thickness, etc.	Low cost and easy to measure but are not fully accurate or validated in different ethnicities
Dual energy X-ray absorptiometry	Generates X-rays at two different energies and uses differential attenuation of the X-ray beam at two energies to measure body composition including fat, fat free mass, and bone mineral density	Highly accurate, relatively low cost, and able to assess whole body but associated with low radiation exposure
Ultrasound	Reflection of ultrasound waves from tissue in the path of the beam	Highly accurate, no radiation exposure, but user-dependent and lack of standardization
Computed tomography scan	Uses X-ray beam and special digital X-ray detectors for generation of cross-sectional imaging with volumetric reconstruction of body adipose tissue and other tissues	Highly accurate and able to assess whole body but with greater radiation exposure and higher cost
Magnetic resonance imaging	Employ powerful magnets, which produce a strong magnetic field that forces protons in the body to align with that field and generate cross-sectional imaging with volumetric reconstruction on the basis of different magnetic properties of water and fat	Provides better soft tissue contrast than other imaging studies and differentiates between fat, water, and muscle better; is able to assess the whole body but has a higher cost, limited access and longer scan times compared with computed tomography and ultrasound
Bioelectrical impedance	Based on the principle that electric current flows at different rates through the body depending upon its composition	Low cost but limited accuracy

[97]. Cardiometabolic health can be enhanced by macronutrients in a low-calorie diet. The DIANA-5 trial investigated the potential of a dietary modification following the principles of macrobiotic and Mediterranean diets to decrease the occurrence of breast cancer-related events. Preliminary findings indicate that the DIANA-5 dietary intervention successfully aids in the reduction of body weight and metabolic syndrome indicators. As per the Obesity Guidelines, a daily energy deficit of 500 - 750 kcal can lead to an average weight loss of 0.5 - 0.75 kg per week. For women, this translates to 1200 - 1500 kcal per day, while for men it is 1500 - 1800 kcal per day [98].

Exercise

Engaging in regular aerobic activities enhances overall fitness and stamina. When paired with a healthy diet, it not only aids in weight loss but also lowers the chances of metabolic syndrome and cardiovascular complications [99-101]. This is achieved by decreasing visceral fat, blood pressure, and lipid levels, and improving glycemic control. Since there is limited long-term data available on weight loss programs, it remains uncertain whether the effects of weight reduction are maintained after the intervention period.

It examined whether physical activity and a healthy diet reduced disease-free survival in 3,643 women with early-stage breast cancer following adjuvant chemotherapy in the SUCCESS C phase 3 randomized trial (Docetaxel based anthracycline free adjuvant treatment evaluation, as well as lifestyle intervention) [102, 103]. The intervention group experienced a notable decrease in initial weight as opposed to the group that did not receive the intervention [104]. In total, 1,477 women successfully finished the 2-year program aimed at improving their lifestyle. A preliminary analysis revealed that those who completed the program had a significantly higher chance of remaining free from disease compared to those who did not (Hazard ratio 0.35). Numerous experiments are currently investigating if incorporating exercise, with or without dietary intervention, can enhance cancer outcomes in survivors who are either overweight or at a healthy weight [105, 106].

Drug therapy

At present, there are only a few medications authorized for the purpose of weight loss. The two most crucial among them are liraglutide and semaglutide, which are analogues of glucagon-like peptide-1 (GLP-1). In a phase 3 trial where liraglutide was administered subcutaneously at a daily dose of 3.0 mg to 3,731 individuals as a supplement to their diet and exercise routine, it resulted in a significant decrease in weight [107, 108]. To illustrate, after 56 weeks of treatment, 63.2% of the patients receiving the medication compared to 27.1% of those receiving a placebo lost a minimum of 5% of their body weight. Additionally, 33.1% of the treated patients, in contrast to 10.6% of the individuals in the control group, experienced a weight loss exceeding 10% [1]. A weekly injection of semaglutide is available. The association between these drugs and thyroid and pancreatic cancer has been demonstrated in a few preclinical studies [109]. According to the studies [153-155], GLP-1 may reduce the risk of prostate and breast cancer by reducing growth. A number of drugs have shown promise in weight loss, including orlistat, phentermine plus topyramine, bupropion and naltrexone, and benzphetamine and phendimetrazine. Although GLP-q analogues do not have side effects, drug interactions, or contraindications like GLP-q, these compounds do have some side effects [110].

Weight reduction surgery

Weight loss surgery or bariatric surgery, such as sleeve gastrectomy, may be beneficial to patients with a BMI of 35 - 40 kg/m^2 and comorbid conditions, such as obstructive sleep apnea. Currently, research indicates that bariatric and related surgeries are safe and will likely be used in the future. Roux-en-Y gastric bypass and sleeve gastrectomy are the most common and most effective types of surgery. Limited evidence indicates that the efficacy of bariatric surgery as a means of weight loss is comparable between cancer survivors and individuals without a cancer history. A comprehensive assessment and meta-analysis of six observational studies encompassing 51,740 patients revealed that bariatric surgery was linked to a 55% decrease in the likelihood of developing cancer [111] (Table 3). Individuals who underwent bariatric surgery for obesity exhibit a 27 - 59% reduced risk of cancer incidence in comparison to controls who were matched for weight and age. Bariatric surgery may only be beneficial for malignancies linked to obesity, including breast and endometrial cancers, where the average risk reduction is 38% (p 0.0001). Compared to those who undergo bariatric surgery who do not develop malignancies related to obesity, bariatric surgery has significantly moderate (9%) risk reductions for lung and bladder cancers; this level of risk reduction is comparable to those who do not undergo bariatric surgery (p = 0.37) [112].

Future Directions

The origins of cancer development and recurrence in relation to obesity are heterogeneous and diverse among various cancer types and remain incompletely comprehended. Further explorations are imperative to fully comprehend the distinct mechanisms underlying each cancer type and to identify potential targets for both primary and secondary cancer prevention. Despite several studies demonstrating a correlation between obesity and unfavorable cancer outcomes, additional research is required using groundbreaking clinical and molecular indicators. This literature has some limitations, including relying on a fixed BMI threshold of 30 kg/m^2 to distinguish obese individuals from non-obese individuals, a lack of information regarding obesity's timing, and a lack of adjustment for psychosocial, genetic, environmental, and behavioral factors [113]. For future research in cancer and obesity, it is imperative to consistently use innovative techniques that offer more accurate evaluations of body fat and its distribution given the limitations of anthropometric measurements.

Ongoing trials around the world are being conducted to gain a better understanding of the correlation between weight loss, physical activity, and the prevention or recurrence of cancer. Known as the Breast Cancer Weight Loss Study, BWEL investigates the impact of weight loss on the survival of early-stage breast cancer patients with a BMI under 27 kg/m^2. The LIVES trial, which stands for Lifestyle Intervention for Ovarian Cancer Enhanced Survival, will examine the effects of diet and exercise on the prognosis of women with advanced stage ovarian cancer [115-116]. Once completed, LIVES will be the largest trial focusing on behavior-based lifestyle interventions for ovarian cancer survivors. The CHALLENGE trial is currently investigating the potential of moderate-intensity physical activity to reduce the risk of cancer recurrence and mortality among colon cancer survivors. The INTERVAL trial will explore the impact of intense aerobic exercise and muscle building on the overall survival of men with advanced prostate cancer [117].

Conclusions

Obesity is a significant global health crisis that can be prevented. It has been linked to various chronic diseases and multiple types of cancer, resulting in higher rates of illness and death. Breast, colorectal, endometrial, esophageal, pancreatic, renal, hepatic, stomach, gallbladder, ovarian, and thyroid cancer, as well as multiple myeloma

and meningioma, are strongly connected to obesity. The exact mechanism by which obesity causes cancer is not fully understood, but it involves adipokines, inflammation, changes in the extracellular matrix, altered metabolism of fatty acids, and the release of insulin-like growth factors and estrogen. To reduce cancer-specific and overall mortality in overweight cancer survivors, weight-reducing strategies are crucial components of cancer care. The primary elements of these strategies include regular exercise, dietary changes, and behavior therapy. Further research is needed to determine the effectiveness and safety of pharmacologic and surgical interventions as major weight reduction strategies for cancer survivors.

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Conflicts of Interest

The authors declare no conflict of interest.

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